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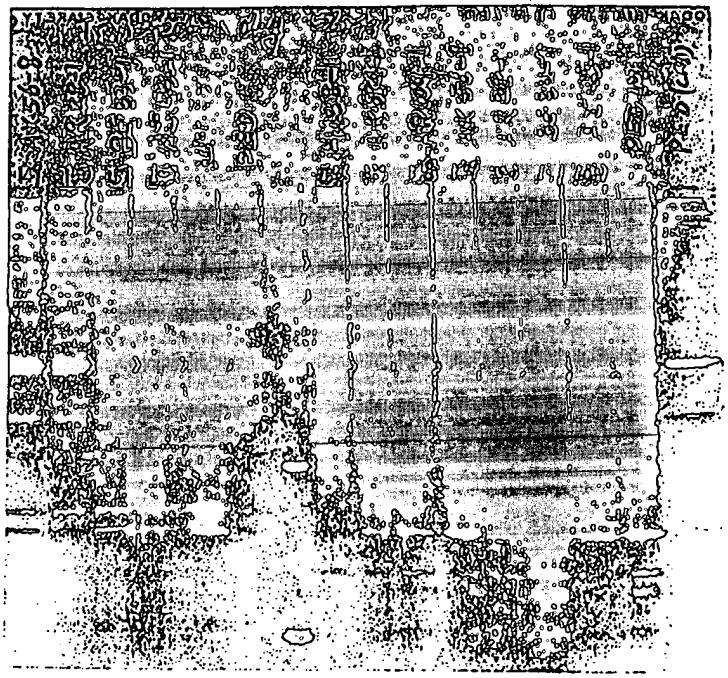
(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 210 to nucleotide 552;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 297 to nucleotide 552;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:3 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:2 from nucleotide 210 to nucleotide 552; the nucleotide sequence of SEQ ID NO:2 from nucleotide 297 to nucleotide 552; the nucleotide sequence of the full length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:2, SEQ ID NO:1 or SEQ ID NO:4 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:3;

(b) fragments of the amino acid sequence of SEQ ID NO:3; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:3.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 31 to nucleotide 180;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:7;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:7 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:6 from nucleotide 31 to nucleotide 180; the nucleotide sequence of the full length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:6, SEQ ID NO:5 or SEQ ID NO:8 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:7;

(b) fragments of the amino acid sequence of SEQ ID NO:7; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:7.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 477 to nucleotide 752;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AX56_8 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AX56_8 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56_8 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56_8 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 477 to nucleotide 752; the nucleotide sequence of the full length protein

coding sequence of clone AX56_8 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AX56_8 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AX56_8 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX56_8 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 262 to nucleotide 594;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 367 to nucleotide 594;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 262 to nucleotide 594; the nucleotide sequence of SEQ ID NO:12 from nucleotide 367 to nucleotide 594; the nucleotide sequence of the full length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 40.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:12, SEQ ID NO:11 or SEQ ID NO:14 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 40;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 40.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 220 to nucleotide 338;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity:

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 220 to nucleotide 338; the nucleotide sequence of the full length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 196 to nucleotide 501;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 196 to nucleotide 501; the nucleotide sequence of the full length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes

the full length or mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 612 to nucleotide 671;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 612 to nucleotide 671; the nucleotide sequence of the full length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 404 to nucleotide 634;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 404 to nucleotide 634; the nucleotide sequence of the full length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 66.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:24;

(b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 66;

(c) fragments of the amino acid sequence of SEQ ID NO:24; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:24 or the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 66.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 161 to nucleotide 553;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 218 to nucleotide 553;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:27 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:26 from nucleotide 161 to nucleotide 553; the nucleotide sequence of SEQ ID NO:26 from nucleotide 218 to nucleotide 553; the nucleotide sequence of the full length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27 from amino acid 1 to amino acid 92.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:26 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:27;

(b) the amino acid sequence of SEQ ID NO:27 from amino acid 1 to amino acid 92;

(c) fragments of the amino acid sequence of SEQ ID NO:27; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:27 or the amino acid sequence of SEQ ID NO:27 from amino acid 1 to amino acid 92.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29 from nucleotide 61 to nucleotide 693;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:30;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:30 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above:

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:29 from nucleotide 61 to nucleotide 693; the nucleotide sequence of the full length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:30 from amino acid 91 to amino acid 130.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:29 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:30;

(b) the amino acid sequence of SEQ ID NO:30 from amino acid 91 to amino acid 130;

(c) fragments of the amino acid sequence of SEQ ID NO:30; and

(d) the amino acid sequence encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:30 or the amino acid sequence of SEQ ID NO:30 from amino acid 91 to amino acid 130.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 165 to nucleotide 857;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:32 from nucleotide 165 to nucleotide 857; the nucleotide sequence of the full length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33 from amino acid 5 to amino acid 115.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:32 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:33;

(b) the amino acid sequence of SEQ ID NO:33 from amino acid 5 to amino acid 115;

(c) fragments of the amino acid sequence of SEQ ID NO:33; and

(d) the amino acid sequence encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:33 or the amino acid sequence of SEQ ID NO:33 from amino acid 5 to amino acid 115.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 290 to nucleotide 652;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:36;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:36 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:35 from nucleotide 290 to nucleotide 652; the nucleotide sequence of the full length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes

the full length or mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:35 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:36;

(b) fragments of the amino acid sequence of SEQ ID NO:36; and

(c) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:36.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 281 to nucleotide 621;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BM46_3 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BM46_3 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46_3 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:39 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:38 from nucleotide 281 to nucleotide 621; the nucleotide sequence of the full length protein coding sequence of clone BM46_3 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BM46_3 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BM46_3 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39 from amino acid 1 to amino acid 79.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:38 or SEQ ID NO:.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:39;

(b) the amino acid sequence of SEQ ID NO:39 from amino acid 1 to amino acid 79;

(c) fragments of the amino acid sequence of SEQ ID NO:39; and

(d) the amino acid sequence encoded by the cDNA insert of clone BM46_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:39 or the amino acid sequence of SEQ ID NO:39 from amino acid 1 to amino acid 79.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF FIGURES

Fig. 1 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein . BG33_7.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences are reported below for each clone and protein disclosed in the present application. In some instances the sequences are preliminary and may include some incorrect or ambiguous bases or amino acids. The actual nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence.

For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Because of the partial ambiguity in reported sequence information, reported protein sequences include "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined nucleotide sequence where applicants believe one should not exist (if the nucleotide sequence were determined more accurately).

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplpasmic reticulum.

Clone "BF245_1"

A polynucleotide of the present invention has been identified as clone "BF245_1". BF245_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BF245_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BF245_1 protein").

The nucleotide sequence of the 5' portion of BF245_1 as presently determined is reported in SEQ ID NO:1. An additional internal nucleotide sequence from BF245_1 as presently determined is reported in SEQ ID NO:2. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:3. Amino acids 1 to 29 of SEQ ID NO:3 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 30. Additional nucleotide sequence from the 3' portion of BF245_1, including the polyA tail, is reported in SEQ ID NO:4.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BF245_1 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for BF245_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. BF245_1 demonstrated at least some homology with an EST identified as "yc91h04.s1 Homo sapiens cDNA clone 23509 3'" (R39256, BlastN) and a human mRNA identified as "KIAA0052" (D29641 (Fasta). Based upon homology, BF245_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AX92_3"

A polynucleotide of the present invention has been identified as clone "AX92_3". AX92_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AX92_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX92_3 protein").

The nucleotide sequence of the 5' portion of AX92_3 as presently determined is reported in SEQ ID NO:5. An additional internal nucleotide sequence from AX92_3 as presently determined is reported in SEQ ID NO:6. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:7. Additional nucleotide sequence from the 3' portion of AX92_3, including the polyA tail, is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX92_3 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for AX92_3 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AX56_8"

A polynucleotide of the present invention has been identified as clone "AX56_8". AX56_8 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AX56_8 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX56_8 protein").

The nucleotide sequence of AX56_8 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX56_8 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. .

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX56_8 should be approximately 730 bp.

The nucleotide sequence disclosed herein for AX56_8 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database. The amino acid sequence of AX56_8 indicates that it may have some homology with chicken cytotactin.

Clone "AS209_1"

A polynucleotide of the present invention has been identified as clone "AS209_1". AS209_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. AS209_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS209_1 protein").

The nucleotide sequence of the 5' portion of AS209_1 as presently determined is reported in SEQ ID NO:11. An additional internal nucleotide sequence from AS209_1 as presently determined is reported in SEQ ID NO:12. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:13. Amino acids 1 to 35 of SEQ ID NO:13 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 36. Additional nucleotide sequence from the 3' portion of AS209_1, including the polyA tail, is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS209_1 should be approximately 3320 bp.

The nucleotide sequence disclosed herein for AS209_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AK684_1"

A polynucleotide of the present invention has been identified as clone "AK684_1". AK684_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. AK684_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AK684_1 protein").

The nucleotide sequence of the 5' portion of AK684_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:16. The predicted acid sequence of the AK684_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Additional nucleotide sequence from the 3' portion of AK684_1, including the polyA tail, is reported in SEQ ID NO:17.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AK684_1 should be approximately 1078 bp.

The nucleotide sequence disclosed herein for AK684_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "AJ168_4"

A polynucleotide of the present invention has been identified as clone "AJ168_4". AJ168_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AJ168_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ168_4 protein").

The nucleotide sequence of AJ168_4 as presently determined is reported in SEQ ID NO:18. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AJ168_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:19. .

The nucleotide sequence disclosed herein for AJ168_4 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AJ168_4 demonstrated at least some homology with an EST identified as "yc79c02.s1 Homo sapiens

cDNA clone 22106 3'" (T65223, BlastN). Based upon homology, AJ168_4 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ143_1"

A polynucleotide of the present invention has been identified as clone "AJ143_1". AJ143_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. AJ143_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ143_1 protein").

The partial nucleotide sequence of AJ143_1, including its 3' end and any identified polA tail, as presently determined is reported in SEQ ID NO:21. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:22. The predicted acid sequence of the AJ143_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22. Additional nucleotide sequence from the 5' portion of AJ143_1 is reported in SEQ ID NO:20.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ143_1 should be approximately 1350 bp.

The nucleotide sequence disclosed herein for AJ143_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database. The amino acid sequence of AJ143_1 indicates that it may show some similarity to phosphoenolpyruvate phosphomutase.

Clone "AC41_1"

A polynucleotide of the present invention has been identified as clone "AC41_1". AC41_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins. AC41_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC41_1 protein").

The nucleotide sequence of the 5' portion of AC41_1 as presently determined is reported in SEQ ID NO:23. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:24. The predicted acid sequence of the AC41_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24. Additional nucleotide sequence from the 3' portion of AC41_1, including the polyA tail, is reported in SEQ ID NO:25.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC41_1 should be approximately 2500 bp.

The nucleotide sequence disclosed herein for AC41_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AC41_1 demonstrated at least some homology with rat developmentally regulated protein (L20319, BlastN). Based upon homology, AC41_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AC222_1"

A polynucleotide of the present invention has been identified as clone "AC222_1". AC222_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins. AC222_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC222_1 protein").

The nucleotide sequence of the 5' portion of AC222_1 as presently determined is reported in SEQ ID NO:26. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:27. The predicted acid sequence of the AC222_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:27. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of AC222_1, including the polyA tail, is reported in SEQ ID NO:28.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC222_1 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for AC222_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. AC222_1 demonstrated at least some homology with a chicken proteoglycan core protein, proteoglycan-Lb (D10485, BlastX). Based upon homology, AC222_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "O289_1"

A polynucleotide of the present invention has been identified as clone "O289_1". O289_1 was isolated from a human dendritic cell cDNA library using methods which are selective for cDNAs encoding secreted proteins. O289_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O289_1 protein").

The nucleotide sequence of the 5' portion of O289_1 as presently determined is reported in SEQ ID NO:29. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:30. The predicted acid sequence of the O289_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:30.

Additional nucleotide sequence from the 3' portion of O289_1, including the polyA tail, is reported in SEQ ID NO:31.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone O289_1 should be approximately 800 bp.

The nucleotide sequence disclosed herein for O289_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "J317_1"

A polynucleotide of the present invention has been identified as clone "J317_1". J317_1 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J317_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J317_1 protein").

The nucleotide sequence of the 5' portion of J317_1 as presently determined is reported in SEQ ID NO:32. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:33. The predicted acid sequence of the J317_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:33. Additional nucleotide sequence from the 3' portion of J317_1, including the polyA tail, is reported in SEQ ID NO:34.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone J317_1 should be approximately 1350 bp.

The nucleotide sequence disclosed herein for J317_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. J317_1 demonstrated at least some identity with EST identified as "ye06h06.r1 Homo sapiens cDNA clone 116987 5'" (T93953, BlastN), "yx58f09.s1 Homo sapiens cDNA clone 265961 3'" (N21491, BlastN) and "yd08h03.s1 Homo sapiens cDNA clone 25214 3'" (R39024, BlastN). Based upon identity, J317_1 proteins and each identical protein or peptide may share at least some activity.

Clone "BG33_7"

A polynucleotide of the present invention has been identified as clone "BG33_7". BG33_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. BG33_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG33_7 protein").

The nucleotide sequence of the 5' portion of BG33_7 as presently determined is reported in SEQ ID NO:35. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:36. The predicted acid sequence of the BG33_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:36. Additional nucleotide sequence from the 3' portion of BG33_7, including the polyA tail, is reported in SEQ ID NO:37.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG33_7 should be approximately 1080 bp.

The nucleotide sequence disclosed herein for BG33_7 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "BM46_3"

A polynucleotide of the present invention has been identified as clone "BM46_3". BM46_3 was isolated from a human adult muscle cDNA library using methods which are selective for cDNAs encoding secreted proteins. BM46_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BM46_3 protein").

The nucleotide sequence of the 5' portion of BM46_3 as presently determined is reported in SEQ ID NO:38. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:39. The predicted acid sequence of the BM46_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:39. Additional nucleotide sequence from the 3' portion of BM46_3, including the polyA tail, is reported in SEQ ID NO:40.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BM46_3 should be approximately 3600 bp.

The nucleotide sequence disclosed herein for BM46_3 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. BM46_3 demonstrated at least some identity with ESTs identified as "zb43c09.s1 Homo sapiens cDNA clone 306352 3'" (N79027, BlastN) and "H. sapiens EST sequence 008-X" (F19321, Fasta). Based upon identity, BM46_3 proteins and each identical protein or peptide may share at least some activity.

Fig. 1 is an autoradiograph evidencing expression of clones of the present invention. All clones were expressed in COS cells.

Deposit of Clones

Clones BF245_1, AX92_3, AX56_8, AS209_1, AK684_1, AJ168_4, AJ143_1, AC41_1, AC222_1, O289_1, J317_1, BG33_7 and BM46_3 were deposited on July 9, 1996 with the American Type Culture Collection under accession number ATCC 98101, from which each clone comprising a particular polynucleotide is obtainable. Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' cite, EcoRI; 3' cite, NotI) to produce the appropriately sized fragment for such clone (approximate clone size fragment are identified below). Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
BF245_1	SEQ ID NO:41
AX92_3	SEQ ID NO:42
AX56_8	SEQ ID NO:43
AS209_1	SEQ ID NO:44
AK684_1	SEQ ID NO:45
AJ168_4	SEQ ID NO:46
AJ143_1	SEQ ID NO:47
AC41_1	SEQ ID NO:48
AC222_1	SEQ ID NO:49
O289_1	SEQ ID NO:50
J317_1	SEQ ID NO:51
BG33_7	SEQ ID NO:52
BM46_3	SEQ ID NO:53

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-

2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried

and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane

domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch

and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation,

Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14. John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober. Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6. Cytokines and their cellular receptors; Chapter 7. Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be

caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural

ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and

BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides . For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated

portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-

Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and

proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of

tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International

Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in

treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober. Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis

Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-

reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat; lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an

antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes.

The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of

the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered

simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 53

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCGGCCGCAG GTCTAGAATT CAATCGGGAG AGAGATACTG CCTGGTTCTT ACAGACACAG 60

ATTATGTCAT CCTTGCAGCC TTCACCCAAA GTTGCTCCCT CCTTCTAGGG CATTTTGTTT 120

TCCTACTTAA TACCAAGTGT CAGCATGTTA GTAATAAACA GGTGTCTCTA CCATTAGTCA 180

AAGGTGGGAG TTAAGCCTTT CATCTTTGTA GCTTTCTCCA GTACCTAACC ATGATTTACT 240

TCATGGGAAG TCCCTCAAAG TACTATTAAT TATCCTGTGT TCTCCTGCCT TGCCTCTTAA 300

CAAAAATTCT GCTGTTCCTG ATTATTTCCA TTTTACCAG 339

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 552 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

AAATANAAAT ANAACAAATT NTAGGGAAGG ACTAAACTGT CTAAAGAAAT GTAAAATCCA 60

AAGACTTGGA TTTTCAACCT ATATCAGAAG ACACTTTTTT TTCAGTTCCC ATGTGAAATT 120

CTTTNTAGGC CAAGGAAGGA CAAATACAAA TTTTGATTAC AAATTATTTT TAGAACTTTG 180

ACACCTACAC TTAAATTCTG AGTCATTAAA CAGGCCTACA TTTATCAACT GTGGAAATAT 240

CAGCCAGTTT TTGCAAACCT CTTCTTAGGA CACTAAGTTG TTTGCAGAAA TCACTAGCAT 300

TGACTGACTC AGCAACAATG TGGTTATATT CTTTGATTAA CTTAGTCCTT TTTCTTGGTC 360

AAGAGTCAGT AGACAGGACT GAAGCTTATG CCCCTTGCCC CCCCACCACC ACTCCATTAC 420

TACCACCTTG GTTTAGCCAT CCTTTTCTTG ATCTGTTCTC CCCACTTCTA CTGTGCTACT 480

CTACAGACTT GCCCTGAATG TAAGAGCAAC AATTACCTTG TAAAGTCCAA GTTGGGGCAG 540

GTCACTCCCA AA 552

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Thr Gly Leu His Leu Ser Thr Val Glu Ile Ser Ala Ser Phe Cys Lys
1 5 10 15

Pro Leu Leu Arg Thr Leu Ser Cys Leu Gln Lys Ser Leu Ala Leu Thr
20 25 30

Asp Ser Ala Thr Met Trp Leu Tyr Ser Leu Ile Asn Leu Val Leu
35 40 45

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TTTTTTNGGA ATCACCAAAA TCAAGNGNGA TATTGTGTTT GCTGCCAGCC TNNANTTGTA 60

GAGTCAGCTA AAGGAATGTG NGATTTTAAA TTATTGACCA CCTGTTTGAT TACAGTTGAN 120

NACAAATGCC TGCAAGTGTG GATTTGGTTT TCCCANACAT TTTAATATGT ATTATATTTA 180

AATCAAACAT CATTCATAGA AAGCATATNA CANANATGTT TANACATAAG CATNACATTT 240

TTTTAATAAA AATGTANACA GGTGGGGCAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 300

AAAAAAAA 308

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 371 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTGGAAACTG TGTTCCCTGC AACCAGTGTG GGCCAGGCAT GGAGTTGTCT AAGGAATGTG 60

GCTTCGGCTA TGGGGAGGAT GCACAGTGTG TGACGTGCCG GCTGCACAGG TTCAAGGAGG 120

ACTGGGGCTT CCAAAAATGC AAGCCCTGTC TGGACTGCGC AGTGGTGAAC CGCTTTCAGA 180

AGGCAAATTG TTCAGCCACC AGTGATGCCA TCTGCGGGGA CTGCTTGCCA NGATTTTATA 240

GGAAGACNAA ACTTGTCGGC TTTCAAAACA TGGAGTGTGT GCCTTGTGGA AACCCTCCTC 300

CTCCTTACGA ACCGCACTGT GCCAGCAAGG TCAACCTCGT GAAAATCNCG TCCACGGCCT 360

CCAGCCCACG G 371

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 181 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGCCTTCATG GCCTAGCTTC CTCTTCAAAA ATGTGTCTAC CTAAGATACT ATTATTTAAG 60

CCTCTGTGTA CTTTTAACCG TAGAACTGAT TTTATAGGAA GACGAAACTT GTCGGCTTTC 120

AAGACATGGA GTGTGTGCCT TGTGGAGACC CTCCTCCTCC TTACGAACCG CACTCTCATC 180

C 181

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Cys Leu Pro Lys Ile Leu Leu Phe Lys Pro Leu Cys Thr Phe Asn
1 5 10 15

Arg Arg Thr Asp Phe Ile Gly Arg Arg Asn Leu Ser Ala Phe Lys Thr
20 25 30

Trp Ser Val Cys Leu Val Glu Thr Leu Leu Leu Leu Thr Asn Arg Thr
35 40 45

Leu Ile
50

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 284 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

AACATTATTA TAATAAACAC CCTCACCANT ACAATNTTCC TAGGAACAAC ATATGACGCA 60

TTNTCCCCTG AANTCNACAC AACATATTTT GTCACCAAGA CCCTANTTCT AACCTCCCTG 120

TTNTTATGAA TTCGAACAGC ANACCCCCGA TTCCGNTACG ACCAANTCAN ACACNTCCTA 180

TGAAAAAANT TCCTACCACT CACCCTAGCA TTACTTATAT GATATGTCTC CANACCCATT 240

ACAATCTCCA GCATTCCCCC TCAAACNTAA AAAAAAAAAA AAAA 284

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1077 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CATTTGATCT TTCCACNACT ATCCAACTCA CAACGTGGCA NTGGGGTTGT GCCGCCTTTG 60

CAGGTGTATA TNANACACGT GGTTTTGGCC GCAGAGGCAC CNGTCGNCAG GTGGGGGGTT 120

CCGCTGCCTG CAAAGGGTCG CTACAGACGT TGTTTGTNTT CAAGAAGCTT CCAGAGGAAN 180

TGCTTCCTTC ACGACATTCA ACAGACCTTG CATTCCTTTG GCGAGAGGGG AAAGACCCCT 240

AGGNATGNTT GTCAAGAAGA CAGGGNCAGG TTTTCCGGCC CTTNACATTG CCAAAAGACG 300

GCAATATGGT GGNAAATAAC ATATAGACAA ACGCACACCG GCCTTATTCC AAGCGGNTTC 360

GGCCAGTAAC GTTAGAATTG CGGCCGCAGG TCTAGAATTC AGTCTTTTCA AGAGAACAAT 420

AAAATAGGCA GTCTCCTACC TCTTGTCTTA CTCTAATATA AACTCCATGA AGATAAGTAT 480

TGTATCCATA CTGTTCATGC TGCACAGCAG TTGCCCTTAT CTGCAGGGCG ACGCATCCCA 540

AGACCCCCAG TGGATGCTTG AAACTGCAGA ANANTNACAC ACGTGATTGC CACCATCGGA 600

ACACATTTCT GTTCACGTCT TCCACCCACA GATTTAATGC CTTTTCCATC TTAACTAAGC 660

ACTCATCATG GACTGTGGCC ATAACTTTTG CAGTTTTAGA TGCAACAGCA AAACTAACAT 720

TAATTTTTTC TTCTTCTTCA CAATTTCATG GGTAGATTTG TTCTTACCGT AGATCTTAKC 780

AACCTCAGCA TATGATGTTT TTTCTTTTGA GAACTTTCAC CTTTTNTCTT AAAGAAAGCA 840

CTTTACAGCT TNTCTTTGGC ATATCTCAAC TGCCAGCATC ACTGNTCTTG AACTTTGGGG 900

CCATTATTAA GTCAGNAAAG GGTTANTTCA AACNAGCTTT TGTANTCCCA CNTACTTGGG 960

AGGNTAAGGC AGGAGAATGG NATGAACCCG AGAGGCAGAG GTTGCAGTGA GCTGAGATCG 1020

TGCCACTGCA CTCCAGCGTG GGTGACAGAG AGATTNTGTC TAAAAAAAAA AAAAAAA 1077

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 92 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Val Leu Tyr Pro Tyr Cys Ser Cys Cys Thr Ala Val Ala Leu Ile Cys
1 5 10 15

Arg Ala Thr His Pro Lys Thr Pro Ser Gly Cys Leu Lys Leu Gln Xaa
20 25 30

Xaa Xaa Thr Arg Asp Cys His His Arg Asn Thr Phe Leu Phe Thr Ser
35 40 45

Ser Thr His Arg Phe Asn Ala Phe Ser Ile Leu Thr Lys His Ser Ser
50 55 60

Trp Thr Val Ala Ile Thr Phe Ala Val Leu Asp Ala Thr Ala Lys Leu
65 70 75 80

Thr Leu Ile Phe Ser Ser Ser Ser Gln Phe His Gly
85 90

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 235 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ATTTCGTACA GTAGGAGATT TCAACAACGT GACAATATTC TCTAGGCACT TGGGCTCACT 60

GTCTGTAGCC CCCACCCCCC GCCTTTCGCC ACCTCCTTGC TTCCCTACTC CCCCTTCTGC 120

TTTTGCCTTT GATGANTTTT TGGCTTACTT TTTGGCGGAG TCTCTTGGAC ACGTTTTTGC 180

TGGTGCTGGA ANATCANATA CATGGAACCT TTGANNNCTG ATTATTTTTC TCCGC 235

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 594 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AGAAACGGTC CATGAACAAT TTGCTACAGG TATAAAGAAG TATCTGCAGA AATCCAGAGC 60

ACTTATTAAA CTTCTTTGAG TTTTNTCAGG AAGATCAANA CAANANGGAG AAATTTTATT 120

AAGATTGGCA AACGCACTGC CTACTTACAG CATAGAGACC CCCAGTGGAG AGCTAGACTG 180

TTTGAATTCC AGAAGGACCA ACACCAGATA AATTATGAAT GTTGAACAAG ATGACCTTAC 240

ATCCACAGCA GAGAATGATA GGTCCTAGGT TTAACAGGGC CCTATTTGAC CCCCTGCTTG 300

TGGTGCTGCT GGCTCTTCAA CTTCTTGTGG TGGCTGGTCT GGTGCGGGCT CAGACCTGCC 360

CTTCNTGTGT GCTCCTGCAG CAACCAGTTC AGCAAGGTGA TTTGTGTTCG GAAAAACCTG 420

CGTGAGGTTC CGGATGGCAT CTCCACCAAC ACACGGCTGC TGAACCTCCA TGAGAACCAA 480

ATCCAGATCA TCAAAGTGAA CAGCTTCAAG CACTTGAGAC ACTTGGAAAT CCTACAGTTG 540

AGTAGGAACC ATATCAGAAC CATTGAAATT GGGGCTTTCA ATGGTCTGGC GAAC 594

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Val Leu Gly Leu Thr Gly Pro Tyr Leu Thr Pro Cys Leu Trp Cys Cys
1 5 10 15

Trp Leu Phe Asn Phe Leu Trp Trp Leu Val Trp Cys Gly Leu Arg Pro
20 25 30

Ala Leu Xaa Val Cys Ser Cys Ser Asn Gln Phe Ser Lys Val Ile Cys
35 40 45

Val Arg Lys Asn Leu Arg Glu Val Pro Asp Gly Ile Ser Thr Asn Thr
50 55 60

Arg Leu Leu Asn Leu His Glu Asn Gln Ile Gln Ile Ile Lys Val Asn
65 70 75 80

Ser Phe Lys His Leu Arg His Leu Glu Ile Leu Gln Leu Ser Arg Asn
85 90 95

His Ile Arg Thr Ile Glu Ile Gly Ala Phe Asn Gly Leu Ala Asn
100 105 110

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

AACAAAGNNC AANATAAAGA ANAGNNCNTA NNCCANTANA GNNAAGAGCC CCNGNACCCC 60

TTATACNAAN AANNAAAAAA AAAAAAAA 88

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 338 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TTCCATTNTG TATTATCACA CCCACCCCCC AATGCCATAC NTTTCTTTCA ATTTAGGATT 60

GTTTNTAGTC AGTCGAGTTT TCCCAGATTG ACTAAGAGTT CCTHMNCTGC CTACTGTAGT 120

CAGCTACANG AACAGTAAAA GAGACCCAGG ACTTGGGCCA GCTGGAAGAC TCAGAAAAAA 180

GTTTCTGTGG GATGCAGACA GCTAAAGAAT GACAATCACA TGCAATTGTC CCAAACCCCA 240

CGTCCGCCCC AAAGGACACC CTCATCTGCC CTTTTCAGAC CCCTTCACAA AGAGCTTCAG 300

GAGCCCTTTT ATGGGGCATC GCCTCTTTGG CCGAATTC 338

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Gln Leu Ser Gln Thr Pro Arg Pro Pro Gln Arg Thr Pro Ser Ser
1 5 10 15

Ala Leu Phe Arg Pro Leu His Lys Glu Leu Gln Glu Pro Phe Tyr Gly
20 25 30

Ala Ser Pro
35

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 118 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TGAGAGCTTC CCAGCTTAGA TTNTGGTGGC TGCATNTGAG AGCTTCCCAG CTTAGATTCT 60

GGTGGGATTG GATCTGGGAG GGGGAAGACC CCAAAAAGCA AAAAAAAAAA AAAAAAAA 118

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 665 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TGGAATTCGG CNTTCATGGC CTARAAAGAR GARCTGGGCG GGGTGGGGGG AARGCGGARG 60

CAGTCTAGTA ATGTAAAGCT CCGCTGARAG GGAGAGTGCC GCCCTAAACA CTCATGCTGC 120

CAGTCCCCAA AAGACTTCAT TCATTCAACA TATATGTGAC CGCCTGCTAC GTGCCAGGCG 180

TGGGCCAGGT CCTAGGGACA AAGGAGAGGC CTCCGCACCC CACCCCATGA CCCATACCTC 240

CTCTTCCCCA CCTCCCTGGG CCAGCCTGCC TTCCTTCTCC CTCCTCCTCC TTCCTGGGGG 300

AAGGAAGCCC CACCTTCTGT GCGCAGTCAG CTCCTAAGCA CGCTCCCGCT TCCCCTGGCC 360

TCCCCATTTA AAAAGGGAGG CAAAGGATGT CACCACTGTC ACTACACTCA TGGCTTTGCT 420

CTGGGAAGTC CTGCAAATAA AATGAAAGTT CTCCAACCCN TCCANACCCA TTNGGGCCAC 480

AAAGGNGAGG GGAGGCAGNT TTGAGGCAGA GGAGCCAGGG CAGGTGCGGC GNTTCCGCTT 540

NTGGTCCCAA AGCAAAGATT CCCCTGNGAC TGACAGCCCG TGTTATGTTA AANACATTTT 600

GTTGGTTTGT AATTCAAATC CCATAAAGCA GGAGGTAGAG AGCCAAAAAA AAAAAAAAAA 660

AAAAA 665

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Gly Gln Arg Arg Gly Leu Arg Thr Pro Pro His Asp Pro Tyr Leu Leu
1 5 10 15

Phe Pro Thr Ser Leu Gly Gln Pro Ala Phe Leu Leu Pro Pro Pro Pro
20 25 30

Ser Trp Gly Lys Glu Ala Pro Pro Ser Val Arg Ser Gln Leu Leu Ser
35 40 45

Thr Leu Pro Leu Pro Leu Ala Ser Pro Phe Lys Lys Gly Gly Lys Gly
50 55 60

Cys His His Cys His Tyr Thr His Gly Phe Ala Leu Gly Ser Pro Ala
65 70 75 80

Asn Lys Met Lys Val
85

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 256 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CNAAAAANAT GAGACCTGGG NTCAGACCTT ACTGTATGAG AAGCAATGCT CCTCAAACCT 60

TCTGCGTGCT GACNTNNACC TTCCCAAAAN CTNNACTGTT GGCGGCGACN TNANCGCTGG 120

AAGCCGAAGG GGAAGANGAG GGAGACNCGA ANCCNGGGCG GTCGGCACTT AGGCGGCGGA 180

CTCGCGGGGG CANCNCCTGC CCGGCCGGGA GCACCACCCA NGGNCCTACN CCAGCGAAGT 240

CCCGCTCCGG CTTCTA 256

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 811 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ANGGCCTTTA TTCCAGNGAA NTCCAAAAAA AAAANAAAGG GNTNNAAGTT TANGTTTTTC 60

NTGAGGCCGC ACCCCCCACT TCCCACNCAG GACNGNACAT NTCNGTGTCT TCNTCCCCCA 120

AATTCCATTA GGGACCCCGA GAACCACCCC AGCTTTCCGG CCACCACAAC AAAGAGCCGC 180

ACCGACCGGC GAGGATAAAC AGCGGCGGAG GGCGAGAGGG CGGCGGGGCG AGCGCCTCCA 240

CGCAGCAACT CCGGAGTCCC CCGCTTGCCC GAGCGCAGNT TCTCCGCTGC TGTTTCCACC 300

GGCTTTGTAA CACTGGGAAT TTACATCCTC ACCCGCACCC CTCACGCCCG AGGATTTTAA 360

ACTCACCTTT ACTCTCGAAC TGAGAGTTGC GGTAGATGGG ATTTTTGCCT TTTCCCCAGA 420

TGGTTGAAGG TTAAGATTTT TGGAAACCCC CCCACCTCCT TATTTCTATT ATTATTTCTG 480

CNAGAAAAGT ATAAAGAGAG TTGTAGTGGA GGTGAGATTT GTGATCGGGA AAGCCTTCGA 540

CTCCCTCCTT CTCCGTCTTC CGCTTCTCTC TCTCTGATTA GTTCCTATCC AGCAGCAGAT 600

TGAANCAGGA GATGATTCTT CTCAAGGTTT GTTCAGCAGC TTCACTTNTA GGCGAAGGCT 660

TCATGAACCA AGTGACNTCA ACCAACAAGG NTTGTTTNTC TNTCCTNTNT CGGAAAAAAA 720

GNGNGAGAAT TGTTNANACC ATTTCAGTTC CAATAATAAA GGACCTATCA GTTCNTAAAG 780

GNGCCAAAAA ANANAAANAA AAAAAAAAAA A 811

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Ile Leu Leu Lys Val Cys Ser Ala Ala Ser Leu Xaa Gly Glu Gly
1 5 10 15

Phe Met Asn Gln
20

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 704 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TNTCAAGCTT GAGGTGTGGC AGGCTTGAGA TTTGGCCAAA CACTNGAGTG ACAATGANAT 60

CCACTTTGCC TTTNTCTCCA CAGGTGTCCA ATCCCAGGTC CAACTGCAGA ATTGGAATTC 120

GGCCTTCATG GCCTACTTCG TTCAAGTGTG AGCTGCGGCT GAGCCCAGCG CTCGAGGCGC 180

GAGGCAGCCA GGAGGGCCCG TGCGGCGCGG GGAGCCASCG AGCGCGCCTT CGGCATTGGC 240

CGCCGCGATG TCAGCTCAGT GCTGTGCGGG CCAGCTGGCC TGCTGCTGTG GGTYTGCAGG 300

CTGCTCTYTY TGCTGTGATT GCTGCCCCAG GATTCGGCAG TCCCTCAGCA CCCGCTTYAT 360

GTACGCCCTC TACTTCATTC TGGTCGTCGT CCTCTGCTGC ATCATGATGT CAACAACCGT 420

GGCTCACAAG ATGAAAGAGC ACATTCCTTT TTTTGAAGAT ATGTGTAAAG GCATTAAAGC 480

TGGTGACACC TGTGAGAAGC TGGTGGGATA TTCTNCCGTG TATAGAGTCT GTTTTGGAAT 540

GGCTTGTTTC TTCTTTATCT TCTGTCTACT GACCTTGAAA ATCAACAACA GCAAAAGTTG 600

TAGAGCTCAT ATTCACAATG GCTTTTGGTT TCTTTAAACT TCTGCTGTTG GGGGCCATGT 660

GCTCAGGAGC TTTCTTCATT CCAGATCAGG ACACCTTTCT GAAC 704

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Met Ser Thr Thr Val Ala His Lys Met Lys Glu His Ile Pro Phe
1 5 10 15

Phe Glu Asp Met Cys Lys Gly Ile Lys Ala Gly Asp Thr Cys Glu Lys
20 25 30

Leu Val Gly Tyr Ser Xaa Val Tyr Arg Val Cys Phe Gly Met Ala Cys
35 40 45

Phe Phe Phe Ile Phe Cys Leu Leu Thr Leu Lys Ile Asn Asn Ser Lys
50 55 60

Ser Cys Arg Ala His Ile His Asn Gly Phe Trp Phe Leu
65 70 75

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 417 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TCCAGTCTTC NTGTTGGNGG AGTTTGCACA TAAGTGGAAC AAGAACTGGT GTGTGCCTTT 60

ATGGAAAGTT CCCATTGACT CACAGAAACT GCCCAGTTTT GACCAAGGCT GNANTCAACT 120

GCATTGCTAG GGATTTGCAG TTTTGTTTCC CTTNANACCT GCTTTTTNGN ACNTCTTCAT 180

NNANTCNTNT CCTTCATTCA CTTNTNACTT TTNGACCCCC TGCCCCNANT CCCTTGCTTG 240

GGTTNTGAGT CAACCAGTGG TGTGAATTAG CCANACTCAA TCCCCTGTTC GTACGGGTTT 300

CGATTTCCTG ACNTNGTGAT CCGCCCACCT CGGCCTCCCA AAGTGCTGGG ATTACAGGCT 360

NGAGCCACCG CACCTGGCCT GATGTTTNTG CAAAAAAAAA AAAAAAAAAA AAAAAAA 417

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 553 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AGGGCCAGGT TTTCCGGGCC NTCACATTGC CAAAAGACGG CAATATGGTG GGAAATAACA 60

TATAGACAAA CGCACACCGG CCTTATTCCA AGCGGNTTCG GCCAGTAACG TTAGAATTGC 120

GGCCGCAGGT YTAGGTCAGA GCCAAAGGAA AGCTTGAAAA ATGAAGACAT TAGCAGGACT 180

TGTTCTGGGA CTTGTCATCT TTGATGCTGC TGTGACTNCC CCAACTCTAG AGTCCATCAA 240

CTATGACTCA GAAACCTATG ATGCCACCTT AGAAGACCTG GATAATTTGT ACAACTATGA 300

AAACATACCT GTTGATAAAG TTGAGATTGA AATAGCCACA GTGATGCCTT CAGGGAACAG 360

AGAGCTCCTC ACTCCACCCC CACAGCCTGA GAAGGCCCAG GAAGAGGAAG AGGAGGAGGA 420

ATCTACTCCC AGGCTGATTG ATGGCTCTTC TCCCCAGGAG CCTGAATTCA CAGGGGTTCT 480

GGGGCCACAC ACAAATGAAG ACTTTCCAAC CTGTCTTTTG TGTACTTGTA TAAGTACCAC 540

CGTGTACTGT GAT 553

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 131 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Lys Thr Leu Ala Gly Leu Val Leu Gly Leu Val Ile Phe Asp Ala
1 5 10 15

Ala Val Thr Xaa Pro Thr Leu Glu Ser Ile Asn Tyr Asp Ser Glu Thr
20 25 30

Tyr Asp Ala Thr Leu Glu Asp Leu Asp Asn Leu Tyr Asn Tyr Glu Asn
35 40 45

Ile Pro Val Asp Lys Val Glu Ile Glu Ile Ala Thr Val Met Pro Ser
50 55 60

Gly Asn Arg Glu Leu Leu Thr Pro Pro Pro Gln Pro Glu Lys Ala Gln
65 70 75 80

Glu Glu Glu Glu Glu Glu Glu Ser Thr Pro Arg Leu Ile Asp Gly Ser
85 90 95

Ser Pro Gln Glu Pro Glu Phe Thr Gly Val Leu Gly Pro His Thr Asn
100 105 110

Glu Asp Phe Pro Thr Cys Leu Leu Cys Thr Cys Ile Ser Thr Thr Val
115 120 125

Tyr Cys Asp
130

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 358 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

TTATAATATA ATGAAAATGT AGTAATTTAA GAAAACACCA GATGAGTTAG GAATAAACCT 60

ATAACATTTA CAAAAAGAGC AAAATTAAGT GATAGAAAAT ATTTCACACA TGTTCTTATA 120

GATCATGTAT CACTTGCAAG TTTTNGGAGT TCATATCCTA TATCATTTCA AATTAAGNAC 180

ATAATAAAGT AAAATTTTGA AATGAACACT TTAGGTATTT TTGCCAAGAT TTAGATGTTT 240

TTAATTAAAC TTTTTTCTTC CTTTTTTTTT CACTAAAGCA TGTTTATTCC CCTAATCCAT 300

TAAAGAGCAT GAAAAAAAGA ATAAATGTAT TTGAAAATTA AAAAAAAAAA AAAAAAAA 358

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 693 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GCGGCCGCTC TANAACTAGT GGATCCCCCG GGCTGCAGGA ATTCGGCCAA AGAGGCCTAG 60

AATGAAAATC CAGGTGTTTG TCATTCATCA GCAACAGGTG ATCCCCATTG CAGGCAGCCG 120

GAACCGACGT CTCCTGGACC ACTGAGCTGG CTGTTCTCAT TACTGCCCTT TCCGCCCAGG 180

CTGGCGGTGA CTCACCGTGA GACAAGTCAG CTAGGTGTTC AGGACAGGGA TTTCAGAGTA 240

TTTTTGTCCA AAGAGGAAAG GGATGATTTC TACGGATCAC TACCAGTTGG TTTACTGTTA 300

GCTCATCGTG TTGATCACAC CAAGTCTTGC CAATTTGGTT TTCTAAGTAT TTTCACGCCT 360

TCTCCTCGTG TCCGCGTCAC TGCTCTGATT CAGGCCCTTG TCATTTCTCA TCTTTGCCAT 420

TTTAGTAGTT TTTGGATTGG GCTCCCGGCT GCTAATTTTG TCCCCTTTTC CACTATCTTC 480

CACATTGTCA CCGCAGTCAT GTTTCTAAGG CAGAATCTCA CTGTGCCCCW CATCGTGTTG 540

CTGGGCCCTT GCATGCCGTA CCCTGGCCTT TGTGAAATGC CCTTCATCTG TGCTCTTCCC 600

TCCACCTGGA ATGTCCGTCT CTCTTTTTCT GCCAACCCAC NCGACCCCTC CCTCCTNCAA 660

GCCCGTGAGT GTCCCCNCCC TCCATGTCCT GTG 693

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 130 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Asn Glu Asn Pro Gly Val Cys His Ser Ser Ala Thr Gly Asp Pro His
1               5                  10                  15

Cys Arg Gln Pro Glu Pro Thr Ser Pro Gly Pro Leu Ser Trp Leu Phe
            20                  25                  30

Ser Leu Leu Pro Phe Pro Pro Arg Leu Ala Val Thr His Arg Glu Thr
        35                  40                  45

Ser Gln Leu Gly Val Gln Asp Arg Asp Phe Arg Val Phe Leu Ser Lys
    50                  55                  60

Glu Glu Arg Asp Asp Phe Tyr Gly Ser Leu Pro Val Gly Leu Leu Leu
65                  70                  75                  80

Ala His Arg Val Asp His Thr Lys Ser Cys Gln Phe Gly Phe Leu Ser
                85                  90                  95

Ile Phe Thr Pro Ser Pro Arg Val Arg Val Thr Ala Leu Ile Gln Ala
            100                 105                 110

Leu Val Ile Ser His Leu Cys His Phe Ser Ser Phe Trp Ile Gly Leu
        115                 120                 125

Pro Ala
    130
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 327 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
TTCGTGGGGC CTGCCCGTTC NGATNTNGNT GCNGCCTCGC TGTCCCCCTC CTCCCTCCNG     60

TGGTTNATAT TCCAGGAATT CTGAATTAGT TGCACCGTGN TCTNATATTT ACTGCAAGAA    120

TAGACCAGTG GTTCTCCAGC TTTTCTGCAC TCTGGAATCA CCTGGGGGTC TTTAAAAAAC    180

ACTGCCTGGC TCCTAGTCCT AAATTTGGAG ATTTAACTGG ACTTACAGTT TTTCAAAGCA    240

CCCCAAAAGA TTNTAATGTG CAGCAAAGTT TGGGAACCAC TGGTATAGAC TGTCTTCTGC    300
```

TTGTTTTCTT GAAAAACACA AACACAA 327

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 857 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

AGACTTGTTG CCAGTGATAC CAAAACAGAC TTTTCCCAAG CAGTGCCTCA CATGTCTGCT 60

GGTGTGGCTT TGGGATTCTC CTGCCCCACC CCCCCGTCCA TGGCAGCCCC CTCCCCAAGG 120

CTTTGCTCAC ACCTGANACA GGAAGGAGGA AGGGGATCCA ATAGGAATAT GGGCCCCGGA 180

GGGGAARTCA TGCACCCCCA AGCCAMCAMC CCCCCCAGCY TTCMASGCAC ATCTCYTGTK 240

TTKGAAKARA RCCAYCCCAA AAAGGGGACA CAGGCTGCCC CGGCCCNTCA ACNGCATCCA 300

CACCCCATCC TCTCATCTTG GGTCCCAGCC AGGCCCCCCC AAAACCAAAG CCCCYTCAAG 360

TCCTGGGGTC CCAGCCTGTG CCCCCAGCTT CCTGCCCACC CAGCCCYGAG CATTCTCACA 420

CAGAGAAAGA ACAAGCAAGG GCTCCAGGGG GACAGGATGG GGCAGGGCAT ACAGTGGGGG 480

GTGGGGGGGC AGMTGGGAGG AGGGAGGGAC AAAACAAAAC ATTTTCCTTT GGGTTTTTTT 540

TTTCTTTCTT TTTTCTCCCC TTTACTCTTT GGGTGGTGTT GCTTTTCCTT TCCTTTTCCC 600

TTTGAGATTT TTTTGTTGTT GTTTCCTTTT TGTATTTTAC TGATATCACC AGGATAGTTT 660

ACTCTCCTTC TAGCTTTCTG CTTACCGCAC ACTGGATAAC ACACACATAC ACACCCACAA 720

AAATGCTCAT GAACCCAATC CGGAGAAGGT TCCAGCAGGT CCCCCACCCT CCCCTCCTCC 780

TCCTACTTCT CCTCTTGACA GCGAGGACAG GAGGGGGACA AGGGGACACC TGGGCAGACC 840

CGCCGGCTCT CCCCCCA 857

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 115 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Glu Tyr Gly Pro Arg Arg Gly Xaa His Ala Pro Pro Ser Xaa Xaa Pro
1 5 10 15

Pro Gln Xaa Ser Xaa His Ile Ser Cys Xaa Xaa Xaa Xaa Pro Xaa Gln
20 25 30

Lys Gly Asp Thr Gly Cys Pro Gly Pro Ser Thr Ala Ser Thr Pro His
35 40 45

Pro Leu Ile Leu Gly Pro Ser Gln Ala Pro Pro Lys Pro Lys Pro Xaa
50 55 60

Gln Val Leu Gly Ser Gln Pro Val Pro Pro Ala Ser Cys Pro Pro Ser
65 70 75 80

Pro Glu His Ser His Thr Glu Lys Glu Gln Ala Arg Ala Pro Gly Gly
85 90 95

Gln Asp Gly Ala Gly His Thr Val Gly Gly Gly Gly Ala Xaa Gly Arg
100 105 110

Arg Glu Gly
115

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60

AAAAAAAAAA AAAAAAAAAA AAAAAA 86

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 652 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TCCTCTGGCT ACTGGGTGCT CGTGGTGCAT TTTACTCGGA GAGAGGCCAT CAAGCAGATC 60

GAGGTGCTGC AGCACGTGGC CACCAACCTG GGGCGCAGCC GTGCCTTCCT TGGAGAGCTA 120

CCTGCGGTTG TTCCARGAGA ACCTGGGCCT GCTGCATAAG TACTACGTCA AGAATGCCCT 180

GGTCTGCAGC CACGATCACC TGACGYTTTT CCTGACCTTG GTGTCCGGGC TAGAGTTCAT 240

TCGTTTCGAG CTGGATCTGG ATGCCCCTTA CCTAGAACTG GCCCCCTACA TGCCCGABTA 300

CTACAAACCT CAGTACCTGN TGGACTTTGA AGACCGCCTT CCCAGCTCGG TCCACGGCTC 360

AGACAGTCTG TCCCTCAANT CTTTCAANTC CGTCACCTCC ACCAACCTGG AGTGGGATGA 420

CAGTGCGATT GCCCCATTTA GTGAGGATGG AGACCTCACA GACACGGTCA GTGGTCCCCG 480

CTCCACAGCC TCCGACCTGA CCAGCAGCAA GGCCTCCACC AGGAGCCCCA CCCAGCGCCA 540

GAACCCCTTN AACGAGGAGC CGGCAGAGAC TGTGTCCTCC TTTGACACCA CCCCCGTGCA 600

CACCACCTTT CAGGAGAAGG NGGAGGCCCA GGCCCTGGAC CCGCCGGANG CC 652

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 121 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Pro Xaa Tyr Tyr Lys Pro Gln Tyr Leu Xaa Asp Phe Glu Asp Arg
1 5 10 15

Leu Pro Ser Ser Val His Gly Ser Asp Ser Leu Ser Leu Xaa Ser Phe
20 25 30

Xaa Ser Val Thr Ser Thr Asn Leu Glu Trp Asp Asp Ser Ala Ile Ala
35 40 45

Pro Phe Ser Glu Asp Gly Asp Leu Thr Asp Thr Val Ser Gly Pro Arg
50 55 60

Ser Thr Ala Ser Asp Leu Thr Ser Ser Lys Ala Ser Thr Arg Ser Pro
65 70 75 80

Thr Gln Arg Gln Asn Pro Xaa Asn Glu Glu Pro Ala Glu Thr Val Ser
85 90 95

Ser Phe Asp Thr Thr Pro Val His Thr Thr Phe Gln Glu Lys Xaa Glu
100 105 110

Ala Gln Ala Leu Asp Pro Pro Xaa Ala
115 120

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 413 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ACTTGTGGAT TTGAAGCCGC TTCCCAGTTC GTTCCAGGGT TCAGACAGTC TGTCCTTCAA 60

TTCTTTCAAT TCCGTCACTT CCACCAACNT GGAGTGGGAT GACAGTGCGA TTGCCCCATN 120

TAGTGAGGAT TATGATTTNG GAGATGTGTT TCCAGCAGTG CNGTCTGNAC CCAGCACAGA 180

TTGGGAAGAT GGAGACNTCA CAGACACGGT CAGTGGTCCC CGTTCCACAG CTTCCGACCT 240

GACCAGCAGC AAGGCTTCCA CCAGGAGCCC CACCCAGCGC CAGAACCCTT TCAANGAGGA 300

GCCGGCAGAG CGTGCACACC ACTTNTCAGG AGAAGGAGGA GGCCCAGGCC CTGGACCCGC 360

CGGATGCCTG CACGGAGNTC GAGGTCATCA GGGTCACCAA AAAAAAAAAA AAA 413

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 621 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ATAACATCTC CCCAGACCCA GAAAAACAGA AAGCTCCACA GAAATTAAAT GTTGAAGAGA 60

AACTCTCAAA GGAAGTTACA GAAGAAAACT ATCTCTTTCC CAGTAAGTTC AGTGGAAAGT 120

GCACTAGAAC ATGAATATGA CTTGGTGAAT TAGATGAAAG TTTTTATGGA CCAGAAAAGG 180

CCACAACATA TTATCTCATC CAGAGACCCA AAGCCAAAAC TCAGCTGACA GGAATGTTTC 240

AAAGGACACA AAGAGAGATG TGGACTCAAA GTCACCGGGG ATGCCTTTAT TTGAAGCAGA 300

GGAAGGAGTT CTATCACGAA CCCAGATATT TCCTACCACT ATTAAAGTCA TTGATCCAGA 360

ATTTCTGGAG GAGCCACCTG CACTTGCATT TTTATATAAG GATCTGTATG AAGAAGCAGT 420

TGGAGAGAAA AAGAAGGAAG AGGAGACAGC TTCTGAAGGT GACAGTGTGA ATTCTGAGGC 480

ATCATTTCCC AGCAGAAATT CTGACACTGA TGATGGAACA GGAATATATT TTGAGAAGTN 540

CATACTCAAA GATGACATTC TCCATGACAC ATCTCTAACT CAAAAGGACC ANGGCCAAGG 600

TCTGGAAAAA AAACAANTTG G 621

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 112 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Met Pro Leu Phe Glu Ala Glu Glu Gly Val Leu Ser Arg Thr Gln Ile
1 5 10 15

Phe Pro Thr Thr Ile Lys Val Ile Asp Pro Glu Phe Leu Glu Glu Pro
20 25 30

Pro Ala Leu Ala Phe Leu Tyr Lys Asp Leu Tyr Glu Glu Ala Val Gly
35 40 45

Glu Lys Lys Lys Glu Glu Glu Thr Ala Ser Glu Gly Asp Ser Val Asn
50 55 60

Ser Glu Ala Ser Phe Pro Ser Arg Asn Ser Asp Thr Asp Asp Gly Thr
65 70 75 80

Gly Ile Tyr Phe Glu Lys Xaa Ile Leu Lys Asp Asp Ile Leu His Asp
85 90 95

Thr Ser Leu Thr Gln Lys Asp Xaa Gly Gln Gly Leu Glu Lys Lys Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 315 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

TCTGTTTTAC TGGTAAAGGA AATCCTCTGA TGGACAGGTC AGAGTGAAGG AAGGTTGTGC 60

TGGTAAGACA TNTCTGANGA AGAGCCATGG ATGCTTTCCA CAAAATGTCA CCTCGCTGCA 120

CTAAAGGATG ATGAATCCTA ATCATTAAAG GAATTGTTTC AGCTGATTTA AATTTATAAT 180

GAACTCTTTT GTAATAATGT ATACTGTAGA ACATGAGTCT CTCCTCCCTA AAATTTTAAA 240

TGTAGAAAAG TGCTATATAT TAGAAATTTC CATTTTGTTA AATAAATGGT TAGAGTCTAT 300

AAAAAAAAAA AAAAA 315

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GNTAAACCAA GGTGGTAGTA ATGGAGTGG 29

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GNAAGCCGAC AAGTTTCGTC TTCCTATAA 29

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GNTCTTGGGA TGCGTCGCCC TGCAGATAA 29

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TNTTGGTGGA GATGCCATCC GGAACCTCA 29

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TGAAGGGGTC TGAAAAGGGC AGATGAG 27

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TNAGTGTAGT GACAGTGGTG ACATCCTTT 29

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TNCCATCTAC CGCAACTCTC AGTTCGAGA 29

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ANTATCCCAC CAGCTTCTCA CAGGTGTCA 29

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GNAGGCATCA CTGTGGCTAT TTCAATCTC 29

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

TNCCTTAGAA ACATGACTGC GGTGACAAT 29

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TCCTCCTACT TCTCCTCTTG ACAGCGA 27

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GNTTGGTGGA GGTGACGGAG TTGAAAGAG 29

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

GNCTCCTCCA GAAATTCTGG ATCAATGAC 29

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 404 to nucleotide 634;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein, which comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium: and

(b) purifying the protein from the culture

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:24;

(b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 66;

(c) fragments of the amino acid sequence of SEQ ID NO:24; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein the protein comprises the amino acid sequence of SEQ ID NO:24.

10. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

11. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 10.

12. The gene corresponding to the cDNA sequence of SEQ ID NO:23 or SEQ ID NO:25.

13. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6 from nucleotide 31 to nucleotide 180;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:7;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:7 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

14. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:7;

(b) fragments of the amino acid sequence of SEQ ID NO:7; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

15. The gene corresponding to the cDNA sequence of SEQ ID NO:6, SEQ ID NO:5 or SEQ ID NO:8 .

16. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 262 to nucleotide 594;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 367 to nucleotide 594;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above : and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

17. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 1 to amino acid 40;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

18. The gene corresponding to the cDNA sequence of SEQ ID NO:12, SEQ ID NO:11 or SEQ ID NO:14 .

19. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 220 to nucleotide 338;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

20. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:15 or SEQ ID NO:17.

22. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 196 to nucleotide 501;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

23. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

24. The gene corresponding to the cDNA sequence of SEQ ID NO:18.

25. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 612 to nucleotide 671;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

26. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

27. The gene corresponding to the cDNA sequence of SEQ ID NO:21 or SEQ ID NO:20.

28. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 165 to nucleotide 857;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

29. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:33;

(b) the amino acid sequence of SEQ ID NO:33 from amino acid 5 to amino acid 115;

(c) fragments of the amino acid sequence of SEQ ID NO:33; and

(d) the amino acid sequence encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

30. The gene corresponding to the cDNA sequence of SEQ ID NO:32 or SEQ ID NO:34.

31. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 290 to nucleotide 652;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:36;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:36 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

32. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

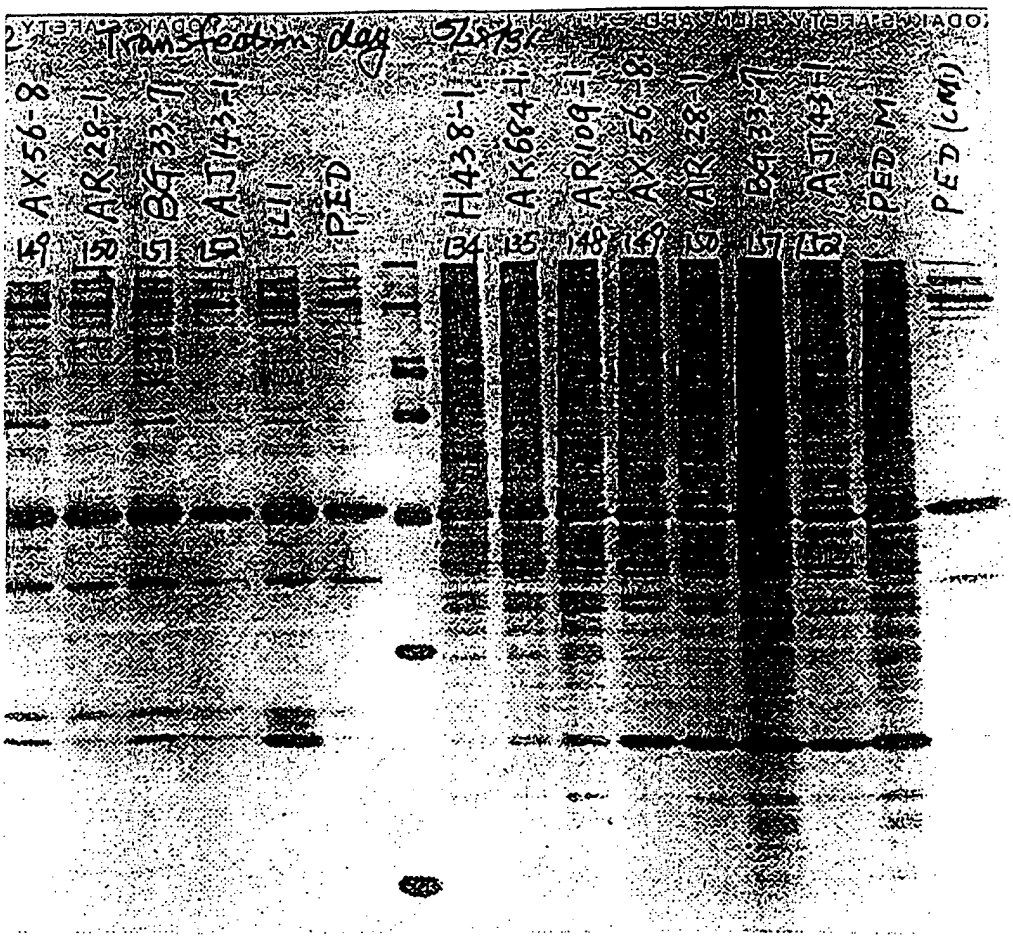
(a) the amino acid sequence of SEQ ID NO:36;

(b) fragments of the amino acid sequence of SEQ ID NO:36; and

(c) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

33. The gene corresponding to the cDNA sequence of SEQ ID NO:35 or SEQ ID NO:37.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AX56-8
AR28-1
BG33-7
AJ143-1
PED
H438-1
AK684-11
AR109-1
AX56-8
AR28-11
BG33-7
AJ143-1
PED M
PED (CM)
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FIGURE 1

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

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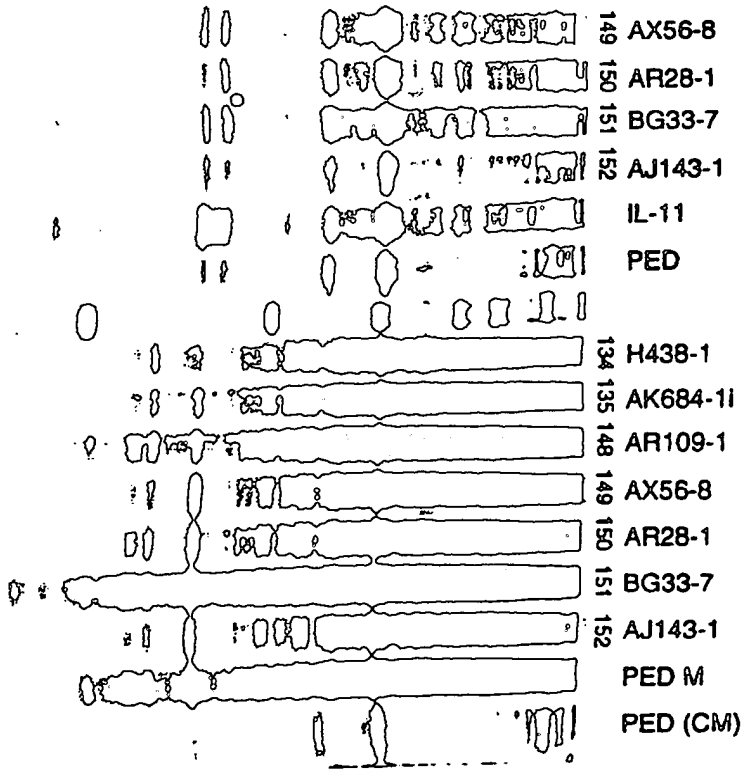
(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



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INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/US 97/11876

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N5/10 C07K14/47 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EMBL SEQUENCE DATABASE, 8 July 1993, HEIDELBERG, BRD, XP002044042 S.S. PFEIFFER: "TPO-1: A developmentally regulated gene expressed during the transition from oligodedroblast to oligodendrocyte" cited in the application Accession no. L20319 ---	1-12
A	NATURE GENETICS, vol. 4, no. 3, pages 256-267, XP000611495 ADAMS M D ET AL: "3,400 NEW EXPRESSED SEQUENCE TAGS IDENTIFY DIVERSITY OF TRANSCRIPTS IN HUMAN BRAIN" see the whole document --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1997	27. 01. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	HORNIG H.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Catogory *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KEYSTONE SYMPOSIUM ON DENDRITIC CELLS: ANTIGEN PRESENTING CELLS OF T AND B LYMPHOCYTES, TAOS, NEW MEXICO, USA, MARCH 10-16, 1995. JOURNAL OF CELLULAR BIOCHEMISTRY SUPPLEMENT 0 (21A). 1995. 19. ISSN: 0733-1959, XP002040894 JACOBS K ET AL: "A novel method for isolating eukaryotic cDNA clones encoding secreted proteins." abstract no. C1-207 see abstract ---	1-12
A	EP 0 510 691 A (OSAKA BIOSCIENCE INST) 28 October 1992 see the whole document ---	1-12
A	WO 94 07916 A (MERCK & CO INC ;SCHMIDT AZRIEL (US); RODAN GIDEON A (US); RUTLEDGE) 14 April 1994 see the whole document ---	1-12
A	WO 90 05780 A (OREGON STATE) 31 May 1990 see the whole document ---	1-12
A	WO 90 14432 A (GENETICS INST) 29 November 1990 see the whole document ---	1-12
A	WO 96 17925 A (IMMUNEX CORP) 13 June 1996 see the whole document ---	1-12
A	MOL. CELL. BIOL., vol. 9, no. 3, March 1989, ASM WASHINGTON, DC,US, pages 1233-1242, XP002041592 R.J. KAUFMAN ET AL.: "Effect of von Willebrand factor coexpression on the synthesis and secretion of factor VIII in chinese hamster ovary cells" see the whole document ---	1-12
A	MOL. CELL. BIOL., vol. 9, no. 3, March 1989, ASM WASHINGTON, DC,US, pages 946-958, XP002041593 R.J. KAUFMAN ET AL.: "The phosphorylation state of eucaryotic initiation factor 2 alters translation efficiency of specific mRNAs" see the whole document --- -/--	1-12

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INTERNATIONAL SEARCH REPORT

Interna il Application No
PCT/US 97/11876

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NUCLEIC ACIDS RESEARCH, vol. 19, no. 16, 1991, IRL PRESS LIMITED,OXFORD,ENGLAND, pages 4485-4490, XP002041594 R.J. KAUFMAN ET AL.: "Improved vectors for stable expression of foreign genes in mammalian cells by use of the untranslated leader sequence from EMC virus" cited in the application see the whole document ---	1-12
P,A	US 5 536 637 A (JACOBS KENNETH) 16 July 1996 see the whole document ---	1-12
P,A	WO 97 07198 A (GENETICS INSTITUT) 27 February 1997 see the whole document ---	1-12
T	WO 97 25427 A (GENETICS INST) 17 July 1997 see the whole document -----	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ıtional application No.
PCT/US 97/ 11876

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation-sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 97/11876

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-12

A composition comprising an isolated polynucleotide selected from the group consisting of: SEQ ID no.23; a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AC41_1; said composition wherein said polynucleotide is operably linked to an expression control sequence; a host cell transformed with said composition; a process for producing a protein which is encoded by said polynucleotide sequence; a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group of SEQ ID no.24, said composition further comprising a pharmaceutical acceptable carrier; a method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of said composition, the gene corresponding to the cDNA sequence of SEQ ID no.23, or SEQ ID no.25.

2. Claims: 13-15

A composition comprising an isolated polynucleotide sequence selected from the group of SEQ ID no.6; a composition comprises a protein, wherein said protein comprises an amino acid sequence selected from the group of SEQ ID no.7; the gene corresponding to the cDNA sequence of SEQ ID no.5, SEQ ID no.6 or SEQ ID no.8;

3. Claims: 16-18

Idem as subject 2 but limited to SEQ ID no.11, SEQ ID no.12, SEQ ID no.13 and SEQ ID no.14.

4. Claims: 19-21

Idem as subject 2 but limited to SEQ ID no.15, SEQ ID no.16, and SEQ ID no.17.

5. Claims: 22-24

Idem as subject 2 but limited to SEQ ID no.18, and SEQ ID no.19.

6. Claims: 25-27

Idem as subject 2 but limited to SEQ ID no.20, SEQ ID no.21, and SEQ ID no.22.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 28-30

Idem as subject 2 but limited to SEQ ID no.32, SEQ ID no.33, and SEQ ID no.34.

8. Claims: 31-33

Idem as subject 2 but limited to SEQ ID no.35, SEQ ID no.36, and SEQ ID no.37.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/US 97/11876

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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